THE COURSE OF EXPERIMENTAL TETANUS INTOXICATION IN ALTERED FUNCTIONAL STATES OF THE CENTRAL NERVOUS SYSTEM

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Among possible experimental approaches to the development of an effective tetanus treatment, an important and promising approach is to explore the possibility of regulating the relation between excitation and inhibition in the cerebral cortex at various stages of the tetanus process.

The significance of inhibition (primarily medicinal and anesthetic) in experimental tetanus has already been examined [4, 8, 10, 11, 13, 16, 19, etc.], but in view of discrepancies in the results the published data do not allow definitive conclusions and necessitate further investigations of the role of strengthening the excitatory and inhibitory processes in the cerebral cortex in tetanus in order to indicate, as far as possible, the future direction of research toward effective treatment of this disease. In studying the role of cortical processes, particularly inhibition, in the development of tetanus intoxication, it is desirable to eliminate such negative properties of hypnotics and general anesthetics as their toxicity, their different effects on different portions of the central nervous system, and their rapid elimination from the organism; in all probability, the last mentioned is accompanied by a change in the relative strength of excitation and inhibition in the cerebral hemispheres, and clearly causes the lack of agreement among published reports.

Accordingly, we thought it would be best to use the method of strengthening inhibition and reducing cortical tone without anaesthetic by "deafferentation" – accomplished by excluding the receptor terminations of the olfactory, visual, and auditory analyzers [1, 2, 3, 7, 9, 12, 15, 18, etc.] – and also by partial decortication of the brain. At the same time, we decided to test the effect of amphetamine sulfate, which strengthens the stimulatory process, stimulates central nervous system activity, and adjusts disturbed relationships between inhibition and excitation in the cerebral cortex [5, 17, etc.].

During the period when these experiments were conducted (1951 – 1956), we were unable to find any indications in the available literature that experimental tetanus had been studied under conditions of exclusion of the olfactory, visual, and auditory analyzers, or administration of amphetamine sulfate.

METHODS AND RESULTS

We performed the first series of experiments on 92 rabbits (47 with excluded olfactory, visual, and auditory analyzers and 45 controls with uninjured analyzers) divided into groups according to the length of time following exclusion of the three distance analyzers and the dose of tetanus toxin. Tetanus toxin was administered to all rabbits via the muscles of the left hip, 6, 29 – 35, and 122 – 183 days after exclusion of the visual and auditory analyzers *.

The results of these experiments showed that after injection of 1 MLD or 1/10 MLD of tetanus toxin at a late period (29th to 35th day, 122nd – 183rd day) or at the earliest period (6th day) after the second step in "deafferentation" (vision and hearing), a distinct retardation of the symptoms of the disease was observed in the first few days of the experiment in all the animals with excluded analyzers as compared with the controls. This is in agreement with published data [4, 11, 14, etc.]. The indicated authors observed that during the first period of development of tetanus intoxication, manifestations of the initial symptom complex of tetanus were absent in animals under amobarbital, chloral hydrate, or ether anaesthesia. We may conclude from this that the inhibitory

* The analyzers were excluded in stages. The olfactory analyzer was excluded first by sectioning and removing the olfactory bulbs; ten days later, the visual and auditory analyzers were excluded by suturing together three tissue layers (rudimentary eyelid, conjunctiva, and skin of eyelid) over the uninjured eyeball, preserving the optic nerve and normal circulation of lacrimal fluid. To exclude the auditory analyzer the tympanic membrane and the auditory ossicles were injured and removed, and the muscles and skin were then sewn in successive layers to the external orifice of the bony portion of the auditory canal.

TABLE 1. Effect of Exclusion of Three Distance Analyzers on Survival Time of Rabbits After Injection of 1 MLD of Tetanus Toxin

Animals	Total number	Number dying in given period of observation			Mean survival time (days)
		1–5 days	6–20 days	after 20th day	
With excluded analyzers . . .	23	14	9	—	6,5
Controls	23	5	16	2	8,7[1]

[1]Mean of observations on 21 rabbits.

process, strengthened in the central nervous system of animals not only by medicinal agents but also by a disturbance of the function of the three distance analyzers, exerts the same retarding influence on the development of the tetanus snydrome in the initial period of the disease.

Further observations established that, as the pathological process develops, marked worsening of the disease and earlier death occurred at the stage of generalization of tetanus in rabbits with excluded analyzers.

Table 1 shows that by the fifth day following injection of 1 MLD of tetanus toxin, 14 out of 23 animals in the group with excluded analyzers had died, and in the control group five out of 23; the mean survival time of animals with excluded analyzers was less (6.5 days) than that of the controls (8.7 days). Injection of 1/10 MLD of toxin usually produced a mild, localized tetanus in normal, unoperated rabbits with subsequent rapid recovery. In "deafferented" animals (with considerably reduced afferentation, in consequence of exclusion of the three distance analyzers), as a result of the injection of the same dose of toxin, the course of intoxication was observed to be milder than in the case of the controls during the first days of the illness; but, later on, the localized tetanus was observed to pass over into a severe generalized form, terminating in death of the overwhelming majority of the "deafferented" animals.

Table 2 shows that following intramuscular injection of 1/10 MLD of tetanus toxin, of 24 rabbits with excluded analyzers only 11 recovered and 13 died of generalized tetanus. In the control group, out of 22 animals only two died, and 20 recovered. The course of tetanus intoxication following injection of 1 MLD and 1/10 MLD of tetanus toxin in animals with excluded distance analyzers was observed to be more severe at 29–35 days after the second stage of "deafferentation" (exclusion of visual and auditory analyzers) than at six days and 122–183 days. It seems to us that this eliminates any question of the significance of operative trauma in the process under consideration.

Thus our data show that prolonged strengthening of inhibition in the cerebral cortex of animals, during the later period of development of tetanus intoxication, exerts a negative effect on the course and outcome of the pathological process. This is in agreement with data in the literature [14, 16, 19].

In our opinion, this conclusion is supported by experiments performed by us on 66 rabbits with ablation of the upper surface of the left cerebral cortex (from the olfactory bulb to the posterior margin of the occipital lobe), and on 63 control (unoperated) rabbits, divided into groups on the basis of postoperative period (6–8, 22–35, 175–186 days), site of injection of the toxin (muscles of the right or left hip), and dose of tetanus toxin (1 and 1/19 MLD).

Experiments conducted under these new conditions of reduced cortical compensatory potentialities showed that the largest effect of decortication on the course and outcome of the tetanus process in rabbits decorticate on the left side is usually noted when they are injected in the limb innervated by the decorticate hemisphere. In such cases, the animals are not only more severely affected with tetanus than the controls, but are also more affected than animals similarly decorticate but receiving the toxin in the opposite limb; they die considerably earlier or recover later.

Thus, whereas after injection of 1 MLD of toxin in the muscles of the right hip rabbits decorticate on the left side die, on the average, after 7.5 days, the corresponding controls die after 11.6–12.4 days and decorticate animals given the same dose of toxin in the muscles of the left hip died after 9.9 days.

Rabbits decorticate on the left side were observed to recover from the injection of 1/10 MLD of tetanus toxin in the muscles of the right hip, on the average, after 32.3 days. Recovery of similarly decorticate animals, injected with the same dose of toxin in the muscles of the left hip, was noted after an average of 22.6 days. Control rabbits that received the same dose of toxin recovered after an average of 20.6–18.7 days.

To generalize from the results of these two series of experiments, we may conclude that strengthening of inhibition and reduction of the compensatory capabilities of the cortex and the work capacity of cortical cells has an aggravating influence on the outcome of tetanus intoxication. This idea gave rise to the supposition that during tetanus, at a certain stage in its development, it would be useful to administer substances that stimulate central nervous system activity. For this purpose we have been testing amphetamine sulfate since 1953.

In the experiments with amphetamine sulfate more than 100 rabbits were used, divided into five groups; these received intramuscular injections of 1, 2, 3, and 12 MLD of tetanus toxin. The experimental animals received amphetamine sulfate intramuscularly in a dose of 1 mg per kg weight, as a rule, at the stage of generalization of the pathological process.

The results of the observations are presented in Table 3. Amphetamine sulfate injected at the stage of generalization of the tetanus syndrome exerted a favor-

TABLE 2. Severity of Tetanus in Rabbits With Excluded Analyzers during the Second Period after Injection of 1/10 MLD of Tetanus Toxin

Animals	Total number	Severity of tetanus process					Number of animals	
		local			generalized		recovered	dead
		mild	moderate	severe	mild	severe		
With excluded analyzers	24	1	6	2	5	10	11	13
Controls	22	7	3	7	5	—	20	2

TABLE 3. Effect of Amphetamine Sulfate on Survival Time of Rabbits Given Various Doses of Tetanus Toxin

Doxe of toxin (MLD's)	Experimental group				Control group	
	experimental group	time of injection of amphetamine sulfate after injection of tetanus toxin	stage of development of tetanus intoxication	mean survival time (days)	number of animals	mean survival time (days)
1	7	Simultaneously with injection, and 24 hrs. after injection	Absence of disease symptoms, localized tetanus	17,0	12	17,5
	4	Six days after injection	Generalized tetanus	40,2		
2	10	4 days	The same	33,5	11	15,1
3	12	3 days	» »	7,1[1]	14	5,7
12	6	2 days	» »	4,8	7	3,3

[1]Excluding one rabbit that was sacrificed on the 84th day after injection of toxin.

able effect on the course of tetanus; the experimental animals lived longer than the controls.

We also observed a favorable effect of amphetamine sulfate therapy when this preparation was injected three to six days after injection of the toxin. Injection of amphetamine sulfate either prior to injection of the animals with lethal doses of toxin, or simultaneously with such injection, or 24 hours afterward had almost no effect. It should be added that combined amphetamine – serotheraphy of rabbits, which received serum and amphetamine sulfate beginning with the third or fourth day after injection of 2 MLD of tetanus toxin, was more effective than serotherapy without amphetamine.

The feature we have noted – that exclusion of the olfactory, visual, and auditory analyzers, as well as administration of amphetamine sulfate, has an effect on various stages of development of the tetanus process in rabbits – can apparently be explained, in our opinion, by an alteration of the functional state of the central nervous system in the course of the development of tetanus. In all probability this assumption is correct. It is supported, first, by the data of E. A. Gromova [6], who showed a change in the electroencephalogram of animals suffering from tetanus, which was characterized by predominance of the stimulatory process in the cerebral cortex at the stage of localized tetanus, and passed over into a predominance of inhibition as the disease became generalized; secondly, by the phenomenon we have observed, that the course of tetanus intoxication is either more severe or more favorable, depending on the stage of its development – probably because of summation of the functional states of the cerebral cortex that have been created (by exclusion of the distance analyzers and by administration of amphetamine sulfate to the animals) and altered in the course of tetanus.

SUMMARY

Tetanus intoxication was much more severe in rabbits with surgical ablation of elements of the left cerebral cortex and in rabbits with three distance analyzers

(olfactory, visual, and auditory) excluded than in controls. Stimulation of central nervous system activity by administration of amphetamine sulfate results in increased resistance to tetanus and prolonged survival time.

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